Asymmetric Catalysis

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Rhodium-Catalyzed Asymmetric Enyne Cycloisomerization of Terminal Alkynes and Formal Total Synthesis of (−)-Platensimycin**

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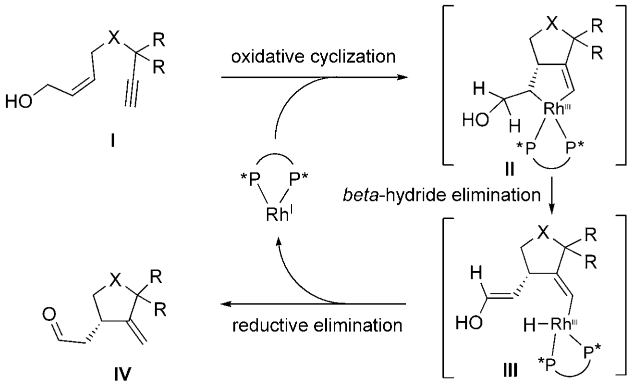
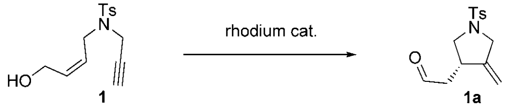
The development of efficient cyclization methods for five-membered ring formation constitutes a continuing challenge in natural and designed molecule construction. Among these methods, the cycloisomerization of 1,6-enynes to form cyclopentane rings has evolved into a powerful technology in chemical synthesis in the past few years. A number of transition metal complexes, such as those of palladium,[1] ruthenium,[2] rhodium,[3] and iron,[4] have proven to be effective catalysts in this transformation. Rhodium-based catalytic systems have attracted particular attention as they demonstrated excellent reactivity and enantioselectivity when applied to internal alkyne substrates.[3] However, in some instances an exocyclic methylene group (as opposed to a substituted olefinic bond) is needed on the resulting intermediates for direct elaboration to more advanced products, a condition that requires terminal alkynes as substrates. Although "capped" alkynes with disposable groups have been utilized in this regard, their removal can be laborious and inefficient. Herein we report a rhodium-catalyzed asymmetric enyne cycloisomerization reaction using terminal alkynes as substrates and its application to a formal total synthesis of (−)-platensimycin.

Scheme 1 shows the proposed mechanism for the rhodium-catalyzed cycloisomerization of the terminal acetylene **I** into a cyclopentane derivative (**IV**) through transient species **II** and **III**.



Scheme 1. Proposed mechanism of rhodium-catalyzed asymmetric cycloisomerization of terminal enynes.

Table 1: Catalyst screening.[a]



Entry	Catalyst	Yield of **1a** [%]	*ee* [%][b]
1	$[Rh(cod)(MeCN)_2]BF_4$,(*S*)-binap	36	90
2	$[\{Rh(cod)Cl\}_2]$, (*S*)-binap, AgOTf	60	91
3	$[\{Rh(cod)Cl\}_2]$, (*S*)-binap, $AgSbF_6$	65	95
4	[Rh((*S*)-binap)]SbF_6	86	>99

[a] Reactions were run in 1,2-dichloroethane (DCE; 0.4 M) in the presence of 5–10 mol% catalyst at 23 °C for 12–16 h. [b] Measured by chiral HPLC methods (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, cod = 1,5-cyclooctadiene, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

Employing 1,6-enyne **1** as a substrate we examined a number of rhodium-based complexes to find the optimum catalytic system; our results are summarized in Table 1. Thus, while the reactivity of $[Rh(cod)(MeCN)_2]BF_4$ in the presence of (*S*)-binap was rather modest (36% yield of product **1a**, after 12 h at 23 °C), the product was obtained with a promising *ee* value (90%, Table 1, entry 1). The complex generated in situ by mixing $[\{Rh(cod)Cl\}_2]$ and AgOTf in the presence of (*S*)-binap led to a 60% product yield and a comparable *ee* value (91%, Table 1, entry 2), whereas the combination of $[\{Rh(cod)Cl\}_2]$, $AgSbF_6$, and (*S*)-binap employed by Zhang et al. with internal alkynes[3] gave **1a** in 65% yield and 95% *ee* (Table 1, entry 3). Finally, it was found that the preformed rhodium catalyst [Rh((*S*)-binap)]SbF_6[5] gave the best results, furnishing product **1a** in 86% yield and greater than 99% *ee* (Table 1, entry 4).

The absolute configuration of product **1a** was determined by X-ray crystallographic analysis of its *p*-bromophenyl carbamate derivative[6] (**1b**, m.p. 99–101 °C, EtOAc/hexanes 1:1) prepared from **1a** through sequential $NaBH_4$ reduction and treatment with *p*-bromophenyl isocyanate in the presence of Et_3N, as shown in Scheme 2.

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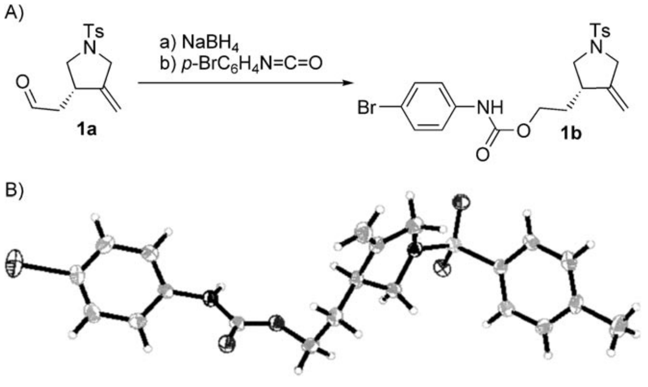
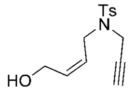
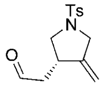
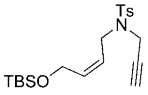
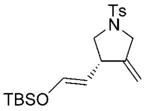
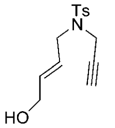
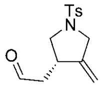
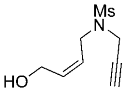
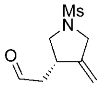
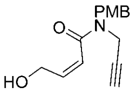
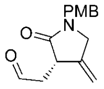
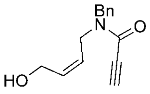
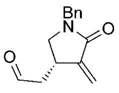
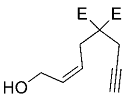
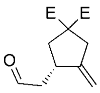
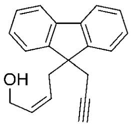
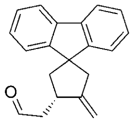
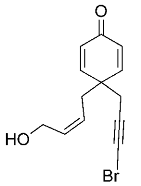
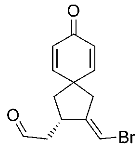
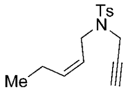
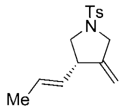
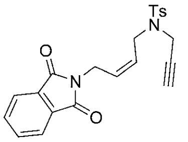
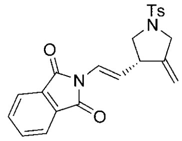


Scheme 2. Preparation (A) and X-ray crystallographic analysis (B) of *p*-bromophenyl carbamate **1b**. Reagents and conditions: a) $NaBH_4$ (1.5 equiv), EtOH, 0 °C, 15 min; b) *p*-bromophenyl isocyanate (1.05 equiv), Et_3N (1.05 equiv), 0 °C, 1 h, 72 % over two steps. Non-hydrogen atoms are shown as 30 % ellipsoids.

Table 2: Asymmetric cycloisomerization reactions.[a]

Entry	Substrate	Product	Yield [%]	*ee* [%]
1	 **1**	 **1a**	86	> 99[b]
2	 **2**	 **2a**	90	97[b]
3	 **3**	 **1a**	45	29[c]
4	 **4**	 **4a**	85	> 98[c]
5	 **5**	 **5a**	75	98[c]
6[d]	 **6**	 **6a**	89	93[b]
7	 **7** E = COOMe	 **7a**	78	97[c]
8[d]	**8** E = COO*i*Pr	**8a**	84	> 98[c]
9[d]	**9** E = SO_2Ph	**9a**	92	87[c]
10	 **10**	 **10a**	85	> 98[c]
11	 **11**	 **11a**	92	> 99[b]
12[d]	 **12**	 **12a**	93	> 98[e]
13[d]	 **13**	 **13a**	83	94[f]

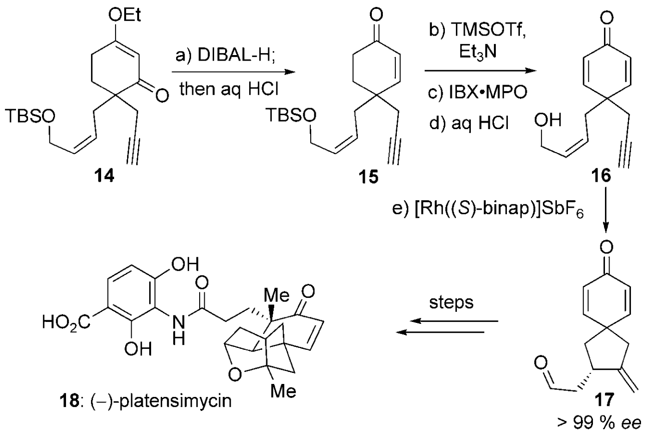
[a] Reactions were run in DCE (0.4 M) in the presence of 10 mol % [Rh((*S*)-binap)]SbF_6 at 23 °C for 12–16 h. [b] Measured by chiral HPLC methods (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester or ethylene glycol acetal. [c] Measured by ^1H and ^{19}F NMR spectroscopic analysis of the corresponding Mosher ester. [d] Reactions were run in acetone as the solvent. [e] Measured by ^1H NMR spectroscopic analysis of the corresponding Mosher ester prepared through sequential dihydroxylation/cleavage, reduction, and esterification. [f] Measured by chiral HPLC methods (OD-H column) after sequential acid hydrolysis, reduction, and derivatization to the corresponding *p*-bromobenzoate ester. Ms = methanesulfonyl, PMB = *para*-methoxybenzyl.

The generality and scope of the developed asymmetric reaction are demonstrated by the results shown in Table 2. In general, most substrates examined led to good yields and excellent *ee* values. The cycloisomerization reaction works well not only with free *cis*-allylic alcohols as demonstrated by most examples in Table 2 (entries 1, 4–11), but also with TBS-protected allylic alcohols, in which case the product with a TBS enol ether moiety is obtained[7] as opposed to the aldehyde (Table 2, entry 2). However, the corresponding *trans*-allylic alcohols are poor substrates as shown with allylic alcohol **3** (Table 2, entry 3). The reaction tolerates a variety of structural motifs, including sulfonamides (Table 2, entries 1–4), lactams (Table 2, entries 5 and 6[8]), 1,1-diesters and sulfones (Table 2, entries 7–9), bis(aromatic) moieties (Table 2, entry 10), and dienones (i.e. Table 2, entry 11). Notably, electron-withdrawing conjugation is tolerated in either π-system of the substrate (Table 2, entries 5 and 6). The example featuring a bromoacetylene expands considerably the scope of this method because of the fertile chemistry of the resulting stereodefined vinyl bromides (Table 2, entry 11).

To explore the feasibility of this asymmetric cycloisomerization reaction with olefinic side chains containing non-oxygen substituents, we examined substrates **12** and **13** (Table 2, entries 12 and 13) having carbon and nitrogen groups, respectively. Indeed, the reaction performs well in both instances and under similar conditions, leading to cycloisomerized products **12a** (Table 2, entry 12, 93 % yield,

> 98 % *ee*)[8] and **13a** (Table 2, entry 13, 83 % yield, 94 % *ee*), respectively.

The power of the present technology was demonstrated by a formal total synthesis of (−)-platensimycin (**18**, Scheme 3) from **14**, an intermediate previously employed in our synthesis of (±)-platensimycin.[9a] Thus, reduction of **14** with DIBAL-H at −78 °C and subsequent exposure to aq HCl at 0 °C led to enone **15** in 88 % overall yield. Conversion of the latter into the corresponding TMS enol ether with subsequent oxidation using IBX·MPO[10] and desilylation (aq HCl) furnished bis(enone) hydroxy enyne **16** in 68 % overall yield. Delightfully, substrate **16** entered the asymmetric cycloisomerization with 5 mol % catalyst ([Rh((*S*)-binap)]SbF$_6$) to afford the desired spiro dienone aldehyde (−)-**17** in 86 % yield and greater than 99 % *ee*. Notably, the use of the in situ generated catalyst (from [{Rh(cod)Cl}$_2$], AgSbF$_6$, and (*S*)-binap) gave erratic results with 10–25 % yield of the desired product. Since (±)-**17** and (−)-**17** have previously been converted into (±)- and (−)-platensimycin,[9] respectively, this streamlined and highly efficient sequence constitutes a formal total synthesis of (−)-platensimycin (**18**).



Scheme 3. Formal total synthesis of (−)-platensimycin. Reagents and conditions: a) DIBAL-H (1.0 M in hexanes, 1.2 equiv), THF, −78→−20 °C, 1 h; then 2 N aq HCl, 0 °C, 30 min, 88 %; b) TMSOTf (1.2 equiv), Et$_3$N (1.5 equiv), CH$_2$Cl$_2$, 0 °C, 30 min; c) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 23 °C, 3 h; d) 1 N aq HCl, THF, 0 °C, 1 h, 68 % over three steps; e) [Rh((*S*)-binap)]SbF$_6$ (0.05 equiv), DCE, 23 °C, 12 h, 86 %, > 99 % *ee*. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl.

The described catalytic asymmetric synthesis complements and expands the scope of the cycloisomerization of 1,6-enynes by offering efficient and direct entries into enantiopure intermediates for complex natural or designed target molecules of biological and medical interest.

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[6] CCDC 723086 (**1b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[7] The ^{1}H NMR spectrum of **2a** revealed the presence of a minor component (ca. 14 %) which appeared to be the *Z*-enol ether isomer of **2a**. ^{1}H NMR (CDCl$_3$, 600 MHz): **2a** (*E*-isomer), δ = 6.28 (d, *J* = 12.0 Hz, 1 H), 4.63 ppm (dd, *J* = 11.9, 9.3 Hz, 1 H); **2a′** (*Z*-isomer), δ = 6.32 (dd, *J* = 5.7, 0.9 Hz, 1 H), 4.19 ppm (dd, *J* = 8.4, 5.8 Hz, 1 H).

[8] A closely related terminal alkynyl-ene substrate was reported in reference [3d] to undergo a rapid cyclization (< 5 min, 100 % conversion) in the presence of a catalytic system generated in situ by sequential mixing of [{Rh(cod)Cl}$_2$], (*S*)-binap, substrate (1 min), and AgSbF$_6$ in DCE at room temperature to afford a related product in poor enantioselectivity (i.e. 6.5 % *ee*, see experimental and footnote 14c in reference [3d]). The key to the success of our protocol is the use of preformed, more well-defined catalyst [Rh ((*S*)-binap)]SbF$_6$. The precise mechanistic differences between the two catalytic systems, however, remain to be elucidated, although the undefined nature of the catalytic species in reference [3d] and the slower reaction rates (12–16 h reaction times at room temperature) under our reaction conditions may be important factors.

[9] a) K. C. Nicolaou, A. Li, D. J. Edmonds, *Angew. Chem.* **2006**, *118*, 7244–7248; *Angew. Chem. Int. Ed.* **2006**, *45*, 7086–7090; b) K. C. Nicolaou, D. J. Edmonds, A. Li, G. S. Tria, *Angew. Chem.* **2007**, *119*, 4016–4019; *Angew. Chem. Int. Ed.* **2007**, *46*, 3942–3945; c) For reviews on the synthesis of platensimycin and related antibiotics, see: K. C. Nicolaou, J. S. Chen, D. J. Edmonds, A. A. Estrada, *Angew. Chem.* **2009**, *121*, 670–732; *Angew. Chem. Int. Ed.* **2009**, *48*, 660–719; K. Tiefenbacher, J. Mulzer, *Angew. Chem.* **2008**, *120*, 2582–2590; *Angew. Chem. Int. Ed.* **2008**, *47*, 2548–2555.

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